LEVEL II

UNITED STATES ARMY ENVIRONMENTAL HYGIENE AGENCY

ABERDEEN PROVING GROUND, MD 21010

(9) Final rept. (+ or -)

(6) SUBCHRONIC INHALATION TOXICITY OF 3-(PHENOXYPHENYL) METHYL (+/-)-CIS, TRANS-3-(2,2-DICHLOROETHENYL) -2,2-DIMETHYLCYCLOPROPANECARBOXYLATE (PERMETHRIN)

MAY-DECEMBER 1978.

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inhalation toxicology
enzyme induction
Beagle dogs
guinea pigs
Sprague-Dawley rats
pulmonary function

20. ABSTRACT (Continue on reverse side if necessary and identify by block number)

The inhalation toxicity of 3-(phenoxyphenyl) methyl (+)-cis, trans-3-(2,2-dichlorcethenyl)-2,2-dimethylcyclopropanecarboxylate (Permethrin) AI3-29158 was determined in rats, beagle dogs, and guinea pigs. They were exposed to the aerosolized test material 6 hours per day for 13 weeks at concentrations of 500, 250, and 125 mg/m^3. The aerosolized technical grade material produced tremors and convulsions in Sprague-Dawley rats at the 500 mg/m^3 concentration. These toxic reactions disappeared by the second week of the study and were not observed in the other test animals. No gross or microscopic compound-related pathological

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changes were observed in the three species. Oxygen consumption was monitored in the rats. No differences from cage controls were found in any test group; urine metabolite studies indicated that the material is rapidly metabolized and excreted. Enzyme induction studies run in postexposure male rats indicated that the group exposed to 500 mg/m^3 had induction of liver enzymes. No permanent changes were observed in dogs, rats or guinea pigs as a result of repeated exposures to aerosols of Permethrin for 6 hours per day, 5 days per week for 13 weeks at concentrations of 500, 250, and 125 mg/m^3.

Ninety-day subchronic inhalation studies in three species resulted in a no effect concentration of 125 mg/m^3.

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DEPARTMENT OF THE ARMY
U. S. ARMY ENVIRONMENTAL HYGIENE AGENCY
ABERDEEN PROVING GROUND, MARYLAND 21010

Mr. Metker/pj/584-3980

HSE-LT/WP

23 APR 1980

SUBJECT: Subchronic Inhalation Toxicity of 3-(Phenoxyphenyl) Methyl (±)-Cis, Trans-3-(2,2-Dichloroethenyl)-2,2-Dimethylcyclopropanecarboxylate (Permethrin), Study No. 75-51-0026-80, May-December 1978

Executive Secretary
Armed Forces Pest Management Board
Forest Glen Section
Walter Reed Army Medical Center
Washington, DC 20012

A summary of the pertinent findings and recommendations of the inclosed report follows:

a. The inhalation toxicity of 3-(phenoxyphenyl) methyl (±)-cis, trans-3-(2,2-dichloroethenyl)-2,2-dimethylcyclopropanecarboxylate (Permethrin) AI3-29158 was determined in three species of laboratory animals. Rats, beagle dogs, and guinea pigs were exposed to the aerosolized test material 6 hours per day for 13 weeks at concentrations of 500, 250 and 125 mg/m^3. The aerosolized technical grade material produced tremors and convulsions in Sprague Dawley rats at the 500 mg/m^3 concentration. These toxic reactions disappeared by the second week of the study and were not observed in the other test animals. No gross or microscopic compound-related pathological changes were observed in the three species. Pulmonary function, clinical chemistries and blood counts were unchanged in the beagle dogs. Oxygen consumption was monitored in the rats throughout the exposure series to assess overall metabolic rate; no differences from cage controls were found in any test group; urine metabolite studies indicated that the material is rapidly metabolized and excreted. Enzyme induction studies run in postexposure male rats indicated that the group exposed to 500 mg/m^3 had induction of liver enzymes, though this effect was not statistically significant at 30 days postexposure or at the lower concentrations tested. No permanent changes were observed in dogs, rats or guinea pigs as a result of repeated exposures to aerosols of Permethrin for 6 hours per day, 5 days per week for 13 weeks at concentrations of 500, 250, and 125 mg/m^3.

b. Ninety-day subchronic inhalation studies in three species resulted in a no effect concentration of 125 mg/m^3. Based on the results of the inhalation studies and the above considerations, it is recommended that AI3-29158 (Permethrin) be approved for further testing and evaluation as a space repellent.

FOR THE COMMANDER:

JOHN F. MAZUR
MAJ, MSC
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as

CF:
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DEPARTMENT OF THE ARMY
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ABERDEEN PROVING GROUND, MARYLAND 21010

HSE-LT/WP

SUBCHRONIC INHALATION TOXICITY OF 3-(PHENOXYPHENYL) METHYL (+)-CIS, TRANS-3-(2,2-DICHLOROETHENYL) -2,2-DIMETHYLCYCLOPROPANECARBOXYLATE (PERMETHRIN) STUDY NO. 75-51-0026-80 MAY-DECEMBER 1978

1. AUTHORITY.

a. Memorandum of Understanding between the Department of the Army; Office of The Surgeon General; the US Army Health Services Command; the US Army Environmental Hygiene Agency; the Armed Forces Pest Control Board; and the US Department of Agriculture, effective December 1970 with Amendment No. 1, effective August 1974.

b. Letter, AFPCB, Armed Forces Pest Control Board, 21 October 1975, subject: Request for Toxicological Evaluation.

c. Letter, AFPCB, Armed Forces Pest Control Board, 5 April 1977, subject: Request for Toxicological Evaluation.

2. REFERENCES.

a. Interim Report, HSE-LT, this Agency, 16 August 1976, Preliminary Assessment of Relative Toxicity of Candidate Insect Repellent AI3-29158, 3-phenoxybenzyl cis, trans 2,2-dimethyl-3-(2,2-dichlorovinyl) cyclopropanecarboxylate, Study No. 51-031-76, December 1975-April 1976.

b. Report, HSE-LT/WP, this Agency, 2 December 1977, Toxicological Evaluation of 3-(phenoxyphenyl) methyl (±)-cis, trans-3-(2,2-dichloroethenyl)-2,2-dimethylcyclopropane carboxylate (Permethrin). Study No. 51-0831-78, December 1975-April 1977 (ADA 047284).

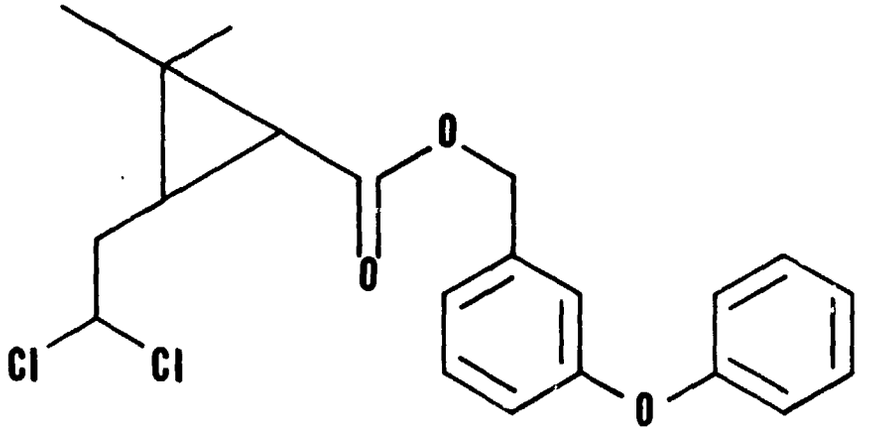
c. Report, HSE-LR-B, this Agency, 24 January 1979, Determination of Urine Metabolite Levels Following Inhalation of the Insecticide Permethrin in Rats, Study No. 75-53-0053-79, May-August 1978.

d. Toxicology Division Procedural Guide, USAEHA, 1979.

Use of trademarked/company names does not imply endorsement by the US Army, but is intented only to assist in identification of a specific compound or instrument.

3. PURPOSE. The purpose of this study was to determine the inhalation toxicity of Permethrin in rats, dogs, and guinea pigs exposed to the aerosolized test compound for a 13-week period. The information from these studies provides a basis for advising the AFPMB on the potential hazards associated with the use of this compound, in accordance with the provisions of the Memorandum of Understanding (reference paragraph 1a).

4. BACKGROUND. Permethrin, ($C_{21}H_{20}Cl_2O_3$, SBP-1513, NRDC 143, FMC 33297, AI3-29158) a synthetic pyrethroid, is an amber liquid with a specific gravity of 1.20, melting point 35°C, boiling point 220°C and is soluble in, or miscible with, most organic solvents. The test material used in this study was provided by S. B. Penick & Co., Orange, NJ, as SBP-1513*, Lot No. RAX-6. The material was identified as Permethrin by the Environmental Chemistry Division using gas chromatography (flame ionization detector). Infrared spectra were also obtained for the compound (Appendix A). The material used had a stated purity of 92.66 percent and a cis/trans ratio of 60/40. The structural formula of this material is shown below.



PERMETHRIN

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*SBP-1513 is a product designation of CPC International Inc., S. B. Penick Co., 100 Church St., New York, NY 10007.

5. PROCEDURES.

a. Materials and Methods. Evaluation of the subchronic inhalation toxicity of Permethrin was conducted by USAEHA using male Hartley guinea pigs, male and female Sprague Dawley rats and male and female beagle dogs. The beagle dogs were purchased from Laboratory Research Enterprises, Kalamazoo, MI; the guinea pigs from Marland Breeding Farms Inc., Hewitt, NJ; and the rats were selected from our own breeding colonies. All animals were maintained on commercially prepared feeds for the duration of the study. Food and water were given ad libitum and the caging facilities were maintained in a 12-hour light-dark sequence. Exposed and control animals were deprived of food and water during the exposure periods. Ambient conditions were 24°C ±2° and 45-55 percent relative humidity. The 13-week inhalation exposures were conducted using 1000 and 2000 liter dynamic flow chambers. The compound was held in glass reservoirs heated to 50°C and aerosolized using Collison nebulizers with dried compressed air at 40 psi. All chambers were sampled at 1-, 3- and 5-hour intervals daily to determine compound concentrations. The three species of laboratory animals were exposed 5 days per week, 6 hours per day for 13 weeks. Male and female rats and dogs and male guinea pigs were observed for development of abnormal signs both during and after exposure. Male guinea pigs were challenged intradermally at the conclusion of the exposure series to determine whether a sensitization reaction could be elicited. Male and female beagle dogs were tested for pulmonary function before the 13-week exposure and blood was drawn weekly for determination of blood chemistries and hematology. At the conclusion of the 13-week exposure, half of the exposed rats were euthanized and submitted for histopathological examination; the remaining rats were held for an additional 90 days prior to submission for histopathologic examination. The beagle dogs were again tested for pulmonary function at the conclusion of the exposure series, euthanized and submitted for histopathology. The male guinea pigs were rested for 14 days at the conclusion of the test, retested for sensitization, and then submitted for necropsy. Selected male rats were tested for oxygen consumption before, during and after the 13-week exposure series.

b. Analytical Procedures.

(1) Biochemical Parameters. Serum clinical chemistries were determined in dogs using the Abbott Bichromatic Analyzer 100 (ABA-100), Abbott Diagnostics, South Pasadena, CA. Red blood cell and plasma cholinesterase activities were determined using the Technicon Autoanalyzer I System, Technicon Corporation, Tarrytown, NY. The Instrumentation Laboratory Flame Photometer Model 143, Instrumentation Laboratory, Inc., Lexington, MA, was used in analyzing for sodium and potassium.

(2) Urine Metabolite Determination.

(a) During the 13th and final week of testing, urine samples were collected daily from four male rats at each exposure concentration. Samples were collected overnight from the end of the exposure period until the animal returned to the exposure chamber the following day (approximately 16 hours) and for 2 days postexposure. Urine volumes were determined and then analyzed for the presence of 3-(2,2-dichlorovinyl)-2,2-dimethylcyclopropanecarboxylic acid (ClVA). Excreted almost exclusively as the glucuronide and sulfate esters, this metabolite is known to appear rapidly in the urine of animals receiving Permethrin orally.[1]

(b) Analysis of the samples for ClVA was by the unpublished method of Cridland and Weatherley.[2] The method involves enzymatic hydrolysis of the Permethrin metabolite, followed by esterification with methanolic boron trifluoride and subsequent analysis of the final product by gas chromatography. Standardization was accomplished using a sample of ClVA generously provided by Dr. James Hubbell of Burroughs-Wellcome Co.

(3) Chamber Concentrations. Ten liter air samples were collected with glass fiber filters followed in series by two midget impingers containing nanograde toluene. A known amount of the internal standard (dioctyl phthalate in hexane) was added to all samples and mixed thoroughly. An aliquot of each of the sample solutions was injected into a Perkin Elmer 3920 gas chromatograph equipped with a flame ionization detector. The instrument was fitted with a 6-ft x 1/8-in stainless steel column packed with Chromosorb® W AW DMCS 80/100 mesh coated with 10 percent UCW 98. The operating parameters were: oven temperature 280°C; inlet temperature 300°C, attenuation 8x10, carrier gas N_2; column flow rate 40 cc/min; H_2 flow 50 cc/min; air flow 550 cc/min. The retention time for dioctyl phthalate was 3.57 min while the retention time of Permethrin was 4.97 min. Peak integrations were calculated using a Hewlett Packard 3352A Laboratory Data System.

c. Physiological Measurements.

(1) Oxygen consumption was monitored in selected groups of male rats using a Collins small animal environmental chamber Model P-2500K and a 1-liter spirometer Model P-2402, Warren E. Collins, Inc., Braintree, MA.

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[1] Gaughan, L. C., T. Unai, and J. E. Casida, "Permethrin Metabolism in Rats" J Agri Food Chem, 25:9 (1977).
[2] Cridland, J. S., and B. C. Weatherley, Wellcome Internal Report 77-2, Wellcome Research Laboratories, Beckenham, England (1977).
® Chromasorb is a registered tradename of Johns Manville, Inc., Denver, CO.

(2) Pulmonary function testing was performed on the beagle dogs before and after the exposure series and was accomplished in the following manner: dogs were anesthetized with Bio-Tal® (Thiamylal sodium), 4.0 percent, by intravenous injection to effect through a pediatric catheter secured in the cephalic vein. A cuffed endotracheal tube was inserted in the trachea and the distal end connected to a Fleisch pneumotachometer for the measurement of airflow. Intrapleural pressure was measured by means of an esophageal balloon. Transpulmonary pressure (the difference between esophageal pressure, and airway pressure derived from a lateral tap at the distal end of the endotracheal tube) was used for all calculations. Both flow and pressure signals were processed in a Buxco Electronics, Inc., Pulmonary Function Computer and the following parameters were recorded on a Honeywell Model 1858 Fiber Optic Recorder: flow, tidal volume, transpulmonary pressure, compliance and resistance. These parameters were measured dynamically on a breath-to-breath basis and averaged every fifth breath.

d. Histopathology. A complete necropsy was performed on all animals that died or became moribund during the test and on all euthanized animals. The following tissues were taken from each animal and fixed in 10-percent neutral buffered formalin: brain, lungs, heart, liver, kidneys, spleen, eyes, bone marrow, trachea, nasal turbinates, thymus, stomach, small intestine, large intestine, pancreas, adrenal glands, urinary bladder, testes, skin, skeletal muscle, and bone. The lungs were infused with formalin and then submerged in the solution for completion of fixation. Sections were prepared from the organs and tissues taken at necropsy, stained with hematoxylin and eosin and examined by light microscopy. Sciatic nerves from selected animals were stained with Luxol Fast Blue myelin stain to assess myelin sheath integrity.

e. Rangefinding Studies. Determination of LC_{50} (4 hours):

(1) Initial rangefinding studies were run using Sprague Dawley rats. The rats (10 male and 10 female, 175-225 g) were exposed in a 200-liter dynamic flow chamber for 4 hours. The compound was held at 50°C and aerosolized with a Collison nebulizer at 40 psi air. A total of 100 rats (20 per concentration level) were exposed at five different concentrations. Results of a Bliss analysis of the data yielded a combined LC_{50} for both males and females of 1.672 g/m^3 95 percent CL ranging from 1.443 g/m^3 to 1.938 g/m^3.

® Bio-Tal is a product of Bio-Ceutic Laboratories, Inc., St Joseph, MO 64502.

(2) Concentrations used in the 13-week study were based on the LC_{50} data and selected at 500, 250 and 125 mg/m^3.

6. RESULTS.

a. Ninety Day Subchronic Study. No compound-related deaths were seen in any of the three species tested over the 13-week test series. Severe tremors and convulsions were noted in the male and female rats at the 500 mg/m^3 concentration level but these signs disappeared by the second week of exposure. The beagle dogs and guinea pigs did not show any toxic signs during the 13-week exposure.

b. Body Weight and Organ-to-Body Weight Ratios.

(1) Weekly body weights of the beagle dogs showed a progressive weight gain throughout the exposure period; grouped data indicated no significant differences between control and exposed groups at the $p=>0.05$ level of significance. Organ-to-body weight ratios at the time of necropsy indicated no significant differences in any test group. These data are shown in Table 1. Similarly, guinea pig growth rates showed no exposure-related effects as shown in Table 2.

(2) The rats were divided into two groups, the first necropsied immediately after the exposure series and the second group held for an additional 90-day period before necropsy. The body weights and organ-to-body weight ratios of the rats are shown in Tables 3 and 4. There were no consistent compound-related effects on body or organ weight parameters in any animals tested.

c. Sensitization Reactions. The guinea pigs used in the study were held for 14 days after the last exposure day and then challenged with Permethrin, 3.0 percent in propylene glycol. Intradermal injections of 0.05 ml were administered to see whether a sensitization reaction could be elicited. Readings were taken at 24 and 48 hours and no sensitization reaction was seen in any test animal at any of the exposure concentrations tested.

d. Clinical Chemistries and Hematology. Blood samples were drawn from the beagle dogs weekly and the following clinical chemistry parameters were run: calcium, sodium, potassium, SGOT, SGPT, GGTP, alkaline phosphatase, BUN cholesterol, triglycerides, LDH, glucose, total protein and bilirubin. No compound-related, statistically significant changes were noted in any of the above parameters as a result of the 13-week inhalation exposure; the results are presented in Tables 5 through 11. Hematological values were also within the normal range during the entire study and are shown in Tables 12, 13 and 14.

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TABLE 1. SUBCHRONIC INHALATION STUDY - BEAGLE DOGS

SUMMARY OF ORGAN-TO-BODY WEIGHT RATIOS

Concentration of Permethrin (mg/M^3)	Terminal Body Weight (kg)	Mean Organ-to-Body Weight Ratios (gms/100gms body weight) + S.D.				
		Liver	Lung	Kidney	Spleen	Testes
Control	12.5 ±1.66	3.17 ± .15	.99 ±.20	.50 ±.08	.54 ±.24	.13 ±.01
500	12.25 ±1.36	3.06 ±.24	1.00 ±.13	.54 ±.07	.62 ±.25	.14 ±.02
250	11.80 ±1.75	3.50 ±.22	.95 ±.09	.57 ±.06	.49 ±.15	.10 ±.01
125	12.60 ±1.29	3.36 ±.46	.99 ±.12	.47 ±.04	.53 ±.18	.15 ±.01

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TABLE 2. SUBCHRONIC INHALATION STUDY - GUINEA PIGS

SUMMARY OF ORGAN-TO-BODY WEIGHT RATIOS

Concentration of Permethrin (mg/M^3)	Terminal Body Weight (kg)	Mean Organ-to-Body Weight Ratios (gms/100gms body weight) ± S.D. Liver	Lung	Kidney	Spleen	Testes
Control	957 ±57	3.60 ±.37	.78 ±.36	.69 ±.08	.14 ±.02	.69 ±.08
500	862 ±137	3.48 ±.26	.61 ±.04	.66 ±.11	.17 ±.04	.72 ±.11
250	907 ±136	3.38 ±.26	.63 ±.12	.63 ±.10	.17 ±.06	.78 ±.10
125	932 ±131	3.37 ±.67	.67 ±.06	.65 ±.05	.17 +.04	.78 ±.12

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TABLE 3. SUBCHRONIC INHALATION STUDY - SPRAGUE DAWLEY RATS

SUMMARY OF ORGAN-TO-BODY WEIGHT RATIOS
(Necropsied after 13-week exposure)

	Concentration of Permethrin (mg/M^3)	Terminal Body Weight (kg)	Mean Organ-to-Body Weight Ratios (gms/100gms body weight) ± S.D. Liver	Lung	Kidney	Spleen	Testes
MALE RATS	Control	487 ±35	3.17 ±.18	.50 ±.15	.68 ±.04	.17 ±.04	.70 ±.07
	500	469 ±21	3.64 ±.21	.55 ±.10	.74 ±.09	.20 ±.06	.77 ±.05
	250	485 ±36	3.26 ±.19	.52 ±.23	.68 ±.07	.16 ±.02	.71 ±.09
	125	518 ±35	3.23 ±.20	.50 ±.13	.70 ±.03	.17 ±.03	.67 ±.05
FEMALE RATS	Control	290 ±29	3.30 ±.26	.68 ±.32	.75 ±.04	.21 ±.05	
	500	290 ±31	3.61 ±.20	.72 ±.19	.72 ±.04	.21 ±.03	
	250	289 ±36	3.42 ±.25	.59 ±.12	.68 ±.04	.21 ±.03	
	125	288 ±12	3.26 ±.21	.77 ±.28	.68 ±.05	.22 ±.05	

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TABLE 4. SUBCHRONIC INHALATION STUDY - SPRAGUE DAWLEY RATS

SUMMARY OF ORGAN-TO-BODY WEIGHT RATIOS
(Necropsied 90 days post exposure)

	Concentration of Permethrin (mg/M^3)	Terminal Body Weight (kg)	Mean Organ-to-Body Weight Ratios (gms/100gms body weight) ± S.D. Liver	Lung	Kidney	Spleen	Testes
MALE RATS	Control	641 ±69	2.85 ±.32	.27 ±.02	.36 ±.04	.58 ±.06	.60 ±.06
	500	656 ±69	3.04 ±.33	.27 ±.03	.32 ±.06	.65 ±.07	.56 ±.06
	250	635 ±50	3.01 ±.26	.31 ±.03	.32 ±.06	.61 ±.06	.62 ±.07
	125	638 ±66	3.01 ±.29	.28 ±.03	.36 ±.03	.63 ±.10	.56 ±.15
FEMALE RATS	Control	321 ±38	2.95 ±.27	.31 ±.03	.61 ±.06	.63 ±.03	
	500	314 ±24	3.14 ±.17	.34 ±.04	.66 ±.05	.69 ±.08	
	250	339 ±33	3.03 ±.17	.32 ±.03	.61 ±.07	.66 ±.06	
	125	337 ±33	3.08 ±.37	.31 ±.04	.60 ±.07	.65 ±.06	

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TABLE 5. SUBCHRONIC INHALATION STUDY - BEAGLE DOGS

Exposure Concentration mg/M³	Pretest Average (8 weeks) Mean ± SD	Week 1	2	3	4	6	8	10	12	14
					SUMMARY OF CALCIUM VALUES (mEq/L)					
Control	10.68 ±0.39	11.03 ±0.28	10.71 ±0.39	10.56 ±0.26	10.47 ±0.21	10.47 ±0.32	10.87 ±0.31	10.13 ±0.41	10.62 ±0.24	10.58 ±0.36
500	10.75 ±0.35	11.17 ±0.44	10.57 ±0.16	10.59 ±0.07	10.68 ±0.26	10.57 ±0.24	10.70 ±0.16	10.05 ±0.20	10.68 ±0.41	10.46 ±0.15
250	10.65 ±0.36	11.02 ±0.64	10.49 ±0.44	10.49 ±0.33	10.44 ±0.53	10.29 ±0.39	10.44 ±0.56	10.01 ±0.40	10.55 ±0.42	10.56 ±0.54
125	10.64 ±0.64	10.88 ±0.34	10.53 ±0.45	10.62 ±0.42	10.52 ±0.28	10.29 ±0.13	10.64 ±0.25	9.97 ±0.21	10.56 ±0.36	10.48 ±0.28
					SUMMARY OF SODIUM VALUES (mEq/L)					
Control	150 ±1.39	151 ±1.73	151 ±0.96	150 ±1.50	147 ±1.4	150 ±1.4	151 ±1.50	144 ±1.5	148 ±0.82	148 ±2.99
500	150 ±1.86	150 ±1.41	150 ±1.71	149 ±1.50	147 ±1.83	150 ±0.58	151 ±2.20	147 ±1.50	149 ±1.15	149 ±2.38
250	150 ±1.44	151 ±1.15	150 ±2.87	149 ±0.82	148 ±1.26	149 ±0.82	151 ±0.96	148 ±0.82	149 ±1.41	148 ±2.06
125	149 ±1.74	150 ±1.29	149 ±0.96	150 ±0.96	147 ±3.27	149 ±1.20	150 ±2.22	147 ±0.0	148 ±.64	149 ±0.58
					SUMMARY OF POTASSIUM VALUES (mEq/L)					
Control	4.8 ±0.27	4.8 ±0.38	5.0 ±0.22	4.5 ±0.17	4.8 ±0.13	4.5 ±0.46	4.9 ±0.26	4.4 ±0.30	4.7 ±0.29	4.7 ±0.40
500	4.9 ±0.25	4.7 ±0.21	4.9 ±0.11	4.7 ±0.45	4.9 ±0.25	5.0 ±0.40	5.0 ±0.16	4.5 ±0.24	4.7 ±0.22	4.6 ±0.25
250	4.8 ±0.28	4.8 ±0.22	4.9 ±0.29	4.7 ±0.33	4.7 ±0.33	4.8 ±0.14	4.9 ±0.37	4.8 ±0.21	4.9 ±0.25	4.9 ±0.29
125	4.8 ±0.35	4.7 ±0.25	4.7 ±0.21	4.7 ±0.50	4.8 ±0.37	4.8 ±0.21	4.9 ±0.50	4.7 ±0.47	4.8 ±0.33	4.8 ±0.36

Study No. 75-51-0026-80, May-Dec 78

TABLE 6. SUBCHRONIC INHALATION STUDY - BEAGLE DOGS

Exposure Concentration mg/M^3	Pretest Average (8 weeks) Mean ± SD	Week 1	2	3	4	6	8	10	12	14
					SUMMARY OF SGOT VALUES (IU/l)					
Control	26.3 ±6.9	27.3 ±3.3	25.0 ±5.5	29.5 ±5.2	32.5 ±6.4	22.8 ±3.6	36.8 ±8.5	29.8 ±4.3	26.3 ±5.1	23.5 ±5.1
500	27.2 ±4.8	24.3 ±1.7	26.8 ±1.7	25.0 ±1.8	29.5 ±3.5	19.8 ±2.9	31.5 ±3.1	47.3 ±23.3	27.8 ±5.7	23.3 ±3.0
250	27.1 ±7.0	26.0 ±2.6	30.0 ±10.4	26.0 ±3.2	29.0 ±7.4	22.8 ±2.8	30.8 ±20.3	30.0 ±4.7	23.3 ±2.1	23.5 ±5.0
125	28.3 ±6.7	26.0 ±4.5	25.8 ±2.9	27.8 ±4.3	32.0 ±8.8	25.5 ±9.5	33.5 ±5.1	30.0 ±13.2	24.7 ±5.0	25.3 ±5.3
					SUMMARY OF SGPT VALUES (IU/l)					
Control	36.8 ±10.8	39.8 ±10.1	38.8 ±11.6	40.8 ±10.6	40.3 ±9.9	36.3 ±7.7	40.5 ±12.4	50.0 ±14.2	41.8 ±12.1	38.3 ±10.8
500	34.4 ±6.8	38.5 ±7.2	34.8 ±4.4	36.5 ±5.1	39.0 ±7.8	32.3 ±4.3	39.5 ±9.0	71.8 ±50.4	40.3 ±11.4	34.8 ±4.3
250	30.3 ±9.6	39.8 ±8.9	37.3 ±11.4	32.8 ±4.9	32.8 ±4.3	27.8 ±6.5	42.5 ±20.8	40.8 ±4.6	34.3 ±7.1	38.8 ±29.1
125	38.6 ±14.0	43.5 ±17.7	39.3 ±10.2	42.3 ±8.0	44.8 ±16.1	44.8 ±19.2	46.3 ±16.2	62.5 ±21.6	47.0 ±18.1	39.3 ±12.0

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TABLE 7. SUBCHRONIC INHALATION STUDY - BEAGLE DOGS

Exposure Concentration mg/M^3	Pretest Average (8 weeks) Mean ± SD	Week 1	2	3	4	6	8	10	12	14
					SUMMARY OF GGPT VALUES (IU/l)					
Control	3.5 ±2.2	0.5 ±0.6	6.0 ±1.2	4.8 ±0.5	5.3 ±1.3	2.5 ±1.7	3.5 ±0.6	5.8 ±1.3	4.0 ±1.4	2.3 ±1.0
500	2.7 ±1.8	0.8 ±1.0	6.0 ±0.0	3.8 ±0.5	4.8 ±1.0	1.5 ±1.3	3.3 ±0.5	4.3 ±0.5	3.3 ±1.0	2.3 ±1.0
250	2.8 ±1.8	1.8 ±0.5	6.0 ±0.8	5.0 ±1.4	4.0 ±1.4	1.5 ±1.0	3.0 ±1.4	4.3 ±1.0	3.8 ±0.9	3.0 ±1.2
125	3.5 ±1.9	2.0 ±1.8	6.0 ±0.0	5.0 ±1.2	4.5 ±0.6	2.0 ±0.8	3.3 ±1.7	5.5 ±0.6	5.2 ±0.5	3.0 ±1.4
					SUMMARY OF ALKALINE PHOSPHATASE VALUES (IU/l)					
Control	103.8 ±21.0	80.8 ±20.5	86.0 ±27.0	89.3 ±27.3	82.5 ±28.6	88.5 ±18.5	70.0 ±23.5	60.8 ±17.6	54.3 ±15.0	72.5 ±31.3
500	96.6 ±22.4	72.0 ±13.2	74.0 ±12.7	76.3 ±15.5	72.8 ±15.3	69.0 ±13.3	71.8 ±21.6	65.0 ±19.1	60.5 ±15.8	62.5 ±17.3
250	91.0 ±18.6	78.3 ±13.0	75.0 ±13.8	73.0 ±15.4	65.0 ±13.1	65.8 ±14.4	65.3 ±17.4	49.3 ±9.1	49.0 ±11.9	56.8 ±22.1
125	99.3 ±17.1	83.8 ±18.0	78.5 ±19.4	76.5 ±15.6	69.3 ±13.4	63.8 ±9.0	57.0 ±11.3	51.3 ±9.6	53.0 ±9.1	54.3 ±10.6

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TABLE 8. SUBCHRONIC INHALATION STUDY - BEAGLE DOGS

Exposure Concentration mg/M^3	Pretest Average (8 weeks) Mean ± SD	Week 1	2	3	4	6	8	10	12	14
					SUMMARY OF BUN VALUES (mg/dl)					
Control	19.0 ±6.1	18.5 ±4.5	24.7 ±1.7	17.4 ±4.6	15.0 ±4.5	13.9 ±5.0	17.2 ±5.6	14.4 ±5.9	15.9 ±4.9	14.7 ±3.7
500	19.5 ±6.7	18.0 ±3.7	19.8 ±3.6	17.7 ±1.3	17.6 ±4.3	21.1 ±8.8	25.5 ±2.1	15.4 ±7.1	18.3 ±5.4	17.2 ±2.2
250	17.1 ±4.6	18.1 ±4.6	17.4 ±4.2	16.4 ±3.4	16.9 ±5.0	20.8 ±7.1	21.3 ±4.3	20.8 ±5.0	20.9 ±4.1	21.0 ±4.5
125	18.5 ±4.5	21.3 ±1.3	22.6 ±2.7	27.2 ±4.1	21.8 ±2.5	18.0 ±3.4	25.0 ±3.4	24.8 ±4.8	26.7 ±6.3	23.4. ±3.0
					SUMMARY OF CHOLESTEROL VALUES (mg/dl)					
Control	166.5 ±26.2	154.3 ±26.1	148.5 ±28.5	150.3 ±20.3	173.5 ±28.9	186.5 ±15.2	171.0 ±5.9	170.3 ±13.7	178.8 ±13.4	180.3 ±15.8
500	167.2 ±29.1	155.5 ±12.3	140.3 ±10.4	150.0 ±12.1	167.8 ±21.6	173.3 ±17.8	168.8 ±23.3	158.8 ±20.8	168.3 ±26.4	151.3 ±12.0
250	178.3 ±40.4	167.3 ±13.7	147.5 ±13.6	155.3 ±9.5	166.0 ±10.2	178.8 ±10.3	180.3 ±14.1	164.5 ±8.9	186.5 ±28.8	201.5 ±60.6
125	184.5 ±26.3	173.8 ±5.6	159.3 ±11.0	177.3 ±14.8	181.5 ±13.6	196.5 ±28.7	181.3 ±20.3	183.3 ±36.7	207.5 ±57.2	187.0 ±60.1

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TABLE 9. SUBCHRONIC INHALATION STUDY - BEAGLE DOGS

Exposure Concentration mg/M^3	Pretest Average (8 weeks) Mean ± SD	Week 1	2	3	4	6	8	10	12	14
					SUMMARY OF TRIGLYCERIDE VALUES (mg/dl)					
Control	85.5 ±33.2	59.5 ±5.9	112.8 ±39.2	72.0 ±22.0	86.3 ±16.8	84.8 ±17.5	104.5 ±30.6	67.0 ±15.4	71.0 ±15.2	70.8 ±35.1
500	135.5 ±224.9	63.5 ±11.1	91.5 ±28.8	70.3 ±12.1	79.5 ±16.3	98.8 ±20.0	136.8 ±30.3	51.3 ±4.8	90.3 ±23.7	57.8 ±16.3
250	69.0 ±23.8	63.8 ±11.3	94.0 ±40.7	117.0 ±59.2	94.0 ±41.0	91.8 ±20.8	124.3 ±37.9	99.0 ±55.4	98.3 ±48.7	67.5 ±27.6
125	78.3 ±28.3	79.0 ±15.0	101.5 ±36.1	130.8 ±51.8	111.0 ±29.3	102.0 ±8.8	118.5 ±12.8	68.8 ±12.8	112.8 ±46.1	85.0 ±32.0
					SUMMARY OF LDH VALUES (IU/l)					
Control	54.6 ±19.9	57.3 ±15.0	52.3 ±9.0	53.8 ±14.6	56.3 ±23.5	46.3 ±18.0	70.5 ±3.5	31.8 ±5.6	61.3 ±31.7	54.3 ±19.4
500	58.8 ±26.3	41.0 ±6.8	51.8 ±8.1	40.0 ±5.5	36.3 ±5.5	34.3 ±12.0	47.7 ±6.7	42.8 ±6.4	51.5 ±23.0	41.3 ±10.4
250	49.9 ±17.3	40.5 ±15.0	59.8 ±22.9	45.8 ±7.1	49.5 ±24.8	37.5 ±8.7	73.8 ±21.6	32.8 ±8.2	40.8 ±5.0	57.3 ±34.8
125	50.3 ±13.8	41.8 ±9.0	47.3 ±5.5	54.3 ±16.7	48.8 ±11.7	39.0 ±3.7	80.3 ±4.5	39.3 ±9.4	39.3 ±9.5	48.3 ±9.7

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TABLE 10. SUBCHRONIC INHALATION STUDY - BEAGLE DOGS

Exposure Concentration mg/M^3	Pretest Average (8 weeks) Mean ± SD	Week 1	2	3	4	6	8	10	12	14
					SUMMARY OF GLUCOSE VALUES (mg/dl)					
Control	111.4 ±7.2	104.0 ±1.8	112.0 ±6.7	118.8 ±4.6	104.0 ±5.0	106.0 ±7.4	104.8 ±7.8	110.5 ±8.4	108.0 ±9.9	99.8 ±5.5
500	104.4 ±20.9	108.3 ±3.2	112.3 ±6.0	114.0 ±6.6	112.5 ±3.7	108.0 ±7.9	107.8 ±0.5	112.5 ±14.5	112.3 ±3.2	105.3 ±4.9
250	110.0 ±9.4	108.3 ±7.8	114.5 ±13.0	123.0 ±8.8	115.5 ±6.9	111.2 ±13.1	114.0 ±9.6	109.0 ±7.3	106.8 ±16.8	108.3 ±8.8
125	112.3 ±6.0	113.5 ±3.7	115.8 ±3.9	118.5 ±5.4	111.0 ±4.0	108.3 ±4.3	112.3 ±6.1	107.3 ±2.9	112.3 ±6.4	107.8 ±5.3
					SUMMARY OF TOTAL PROTEIN VALUES (g/dl)					
Control	6.00 ±0.36	5.58 ±0.11	5.64 ±0.02	5.97 ±0.15	5.61 ±0.13	5.76 ±0.17	5.96 ±0.08	5.91 ±0.20	5.89 ±0.40	6.37 ±0.21
500	5.83 ±0.42	5.50 ±0.22	5.41 ±0.14	5.87 ±0.13	5.80 ±0.27	5.80 ±0.36	5.93 ±0.13	5.87 ±0.41	5.90 ±0.39	5.93 ±0.29
250	5.99 ±0.35	5.64 ±0.33	5.56 ±0.26	5.96 ±0.59	5.56 ±0.26	5.80 ±0.31	6.47 ±1.10	6.13 ±0.28	6.06 ±0.24	6.39 ±0.56
125	5.92 ±0.32	5.53 ±0.15	5.61 ±0.32	6.20 ±0.46	5.50 ±0.30	5.78 ±0.17	5.91 ±0.45	5.97 ±0.38	6.09 ±0.58	6.03 ±0.13

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TABLE 11. SUBCHRONIC INHALATION STUDY - BEAGLE DOGS

Exposure Concentration mg/M^3	Pretest Average (8 weeks) Mean ± SD	Week 1	2	3	4	6	8	10	12	14
					SUMMARY OF TOTAL BILIRUBIN VALUES (mg/dl)					
Control	0.38 ±0.17	0.23 ±0.10	0.45 ±0.13	0.38 ±0.10	0.30 ±0.12	0.28 ±0.10	0.53 ±0.19	0.38 ±0.10	0.28 ±0.10	0.40 ±0.18
500	0.37 ±0.16	0.23 ±0.05	0.28 ±0.10	0.28 ±0.05	0.28 ±0.10	0.40 ±0.12	0.60 ±0.14	0.33 ±0.05	0.30 ±0.14	0.38 ±0.10
250	0.32 ±0.13	0.23 ±0.13	0.43 ±0.22	0.30 ±0.08	0.40 ±0.22	0.38 ±0.10	0.55 ±0.24	0.43 ±0.15	0.45 ±0.26	0.45 ±0.17
125	0.32 ±0.10	0.20 ±0.06	0.33 ±0.10	0.53 ±0.21	0.38 ±0.15	0.33 ±0.05	0.48 ±0.10	0.38 ±0.15	0.43 ±0.15	0.48 ±0.15

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TABLE 12. SUBCHRONIC INHALATION STUDY - HEMATOLOGY VALUES - BEAGLE DOGS

Hematological Determination	Exposure Concentration (mg/M^3)	Pretest Average (8 weeks) Mean ± SD	WEEK 1	2	3	4	6	8	10	12	14
$RBCx10^6/mm^3$	Control	6.28 ±0.29	6.27 ±0.13	6.31 ±0.41	6.24 ±0.39	6.28 ±0.15	6.21 ±0.22	6.63 ±0.48	6.50 ±0.38	6.25 ±0.20	6.72 ±0.20
	500	6.44 ±0.37	6.27 ±0.26	6.30 ±0.25	6.24 ±0.02	6.60 ±0.39	6.42 ±0.44	6.91 ±0.11	6.84 ±0.14	6.64 ±0.23	6.86 ±0.13
	250	6.57 ±0.47	6.49 ±0.72	6.76 ±0.66	6.54 ±0.84	6.80 ±1.15	6.49 ±0.86	7.10 ±0.89	7.10 ±0.57	6.72 ±0.4	6.69 ±0.35
	125	6.40 ±0.30	6.37 ±0.16	6.54 ±0.36	6.50 ±0.24	6.37 ±0.41	6.43 ±0.36	6.83 ±0.38	6.82 ±0.41	6.49 ±0.14	6.68 ±0.16
Mean Cell Volume (μ^3)	Control	71 ±2.0	72 ±3.3	71 ±2.6	71 ±2.6	72 ±2.1	70 ±2.8	69 ±2.3	69 ±2.3	69 ±1.0	70 ±2.4
	500	70 ±1.4	71 ±1.5	71 ±1.2	71 ±1.2	71 ±1.5	70 ±1.3	68 ±1.3	69 ±1.6	69 ±2.2	72 ±3.6
	250	70 ±2.0	71 ±1.9	71 ±2.5	71 ±2.6	71 ±1.9	71 ±0.5	69 ±2.9	69 ±2.6	68 ±2.2	70 ±2.1
	125	70 ±1.8	70 ±1.3	71 ±0.8	71 ±1.3	69 ±1.3	68 ±1.3	68 ±1.3	69 ±1.4	69 ±1.7	69 ±1.4

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TABLE 13. SUBCHRONIC INHALATION STUDY - HEMATOLOGY VALUES - BEAGLE DOGS

Hematological Determination	Exposure Concentration (mg/M^3)	Pretest Average (8 weeks) Mean ± SD	WEEK 1	2	3	4	6	8	10	12	14
Hematocrit %	Control	44.4 ±2.8	44.8 ±1.7	45.0 ±3.4	44.2 ±1.6	44.7 ±2.0	42.9 ±2.6	45.8 ±3.5	44.6 ±3.1	43.1 ±1.2	42.1 ±1.0
	500	44.6 ±2.8	44.5 ±1.6	44.7 ±1.4	44.0 ±0.6	47.0 ±3.2	44.1 ±3.8	47.1 ±1.1	46.9 ±1.3	45.6 ±2.0	49.1 ±2.5
	250	45.9 ±3.0	45.5 ±4.1	47.6 ±3.5	45.8 ±4.7	47.6 ±7.3	45.2 ±6.0	48.4 ±4.5	48.4 ±2.3	45.7 ±2.6	46.5 ±1.8
	125	44.6 ±2.6	44.5 ±1.5	45.8 ±2.3	45.4 ±1.4	44.5 ±2.5	43.6 ±3.0	46.3 ±3.0	46.4 ±3.5	44.2 ±1.9	46.0 ±1.5
WBCx$10^3/mm^3$	Control	12.5 ±2.6	11.4 ±3.2	12.1 ±1.2	9.9 ±1.5	11.0 ±1.6	12.8 ±3.5	13.7 ±4.1	13.1 ±3.6	11.5 ±2.6	12.2 ±2.4
	500	15.7 ±3.7	15.6 ±3.1	14.0 ±4.0	12.9 ±2.8	14.5 ±3.4	13.5 ±4.2	15.8 ±2.5	14.0 ±3.2	15.2 ±3.5	14.5 ±5.9
	250	13.9 ±4.6	12.0 ±4.3	12.1 ±4.0	13.5 ±5.0	13.8 ±5.1	13.9 ±4.1	15.8 ±6.1	14.8 ±4.8	13.1 ±4.8	12.7 ±5.0
	125	12.5 ±2.0	11.4 ±1.8	12.2 ±4.0	11.4 ±2.7	12.9 ±2.3	12.1 ±2.2	13.4 ±1.2	11.7 ±1.0	12.4 ±2.5	12.3 ±2.1

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TABLE 14. SUBCHRONIC INHALATION STUDY - HEMATOLOGY VALUES - BEAGLE DOGS

Hematological Determination	Exposure Concentration (mg/M^3)	Pretest Average (8 weeks) Mean ± SD	WEEK 1	2	3	4	6	8	10	12	14
Hemoglobin gm/dl	Control	15.3 ±0.89	15.5 ±0.48	15.5 ±1.26	15.2 ±0.67	15.5 ±0.57	15.7 ±1.08	16.0 ±1.35	15.5 ±0.97	15.4 ±0.39	16.3 ±0.67
	500	15.8 ±1.19	15.8 ±0.85	15.6 ±0.92	15.4 ±0.41	16.5 ±0.42	16.3 ±0.75	17.0 ±0.44	16.7 ±0.52	16.7 ±0.71	16.7 ±0.63
	250	15.9 ±0.83	16.4 ±1.5	16.7 ±1.37	16.2 ±2.10	16.3 ±2.47	16.6 ±1.53	17.2 ±1.87	17.3 ±0.77	16.8 ±1.05	16.4 ±0.59
	125	15.6 ±0.81	16.1 ±0.40	16.2 ±0.76	16.3 ±0.62	15.6 ±0.78	16.2 ±0.80	16.6 ±0.83	16.5 ±0.80	16.5 ±0.44	16.2 ±0.55

e. Pulmonary Function Tests. Pulmonary function data consisted of five parameters: Tidal Volume, Minute Volume, Transpulmonary Pressure, Compliance and Resistance. The beagle dogs showed great variability in their individual measured values but all fell within reported limits.[3] Post exposure measurements were not statistically different from preexposure values and are shown in Table 15. There is, however, a definite trend toward lower compliance and higher resistance in the exposed groups. The significance of this finding is complicated by the incidence and severity of pneumonia in these animals as shown in Appendices E-3 and E-4.

f. Oxygen Consumption Studies. A selected group of five male rats from each exposure group were monitored for oxygen consumption as a means of determining their overall metabolic state during exposure to Permethrin. Each group of five rats was tested for a 15-minute period prior to exposure and immediately post exposure on the Monday and Friday of each week during the 13-week exposure. Oxygen consumption was consistent for the four groups tested and no significant differences were detected between control and test groups. Results of the study as presented in Figure 1 indicate a gradual decrease in oxygen consumption as the animals aged but this is similar for all four groups. Each data point plotted represents the weekly mean value of the group and is expressed in milliliters of oxygen per kilogram per day. Results of this study indicate that the rats' metabolism as judged by oxygen consumption was normal throughout the study and was unaffected by the inhalation of the Permethrin aerosol.

g Urine Metabolite Studies. The pattern of metabolite excretion indicates that the rat has an extremely efficient mechanism for metabolizing this compound. Results of the study are shown in Figure 2. It is apparent from the plot that the levels of metabolite rise as the weekly exposure continues and tail off very rapidly when exposure is terminated. It is obvious from the plot that the 500 mg/m^3 concentration produced urine metabolite levels three to four times as great as the lower concentrations. A surprising observation was that the animals receiving the lower exposure concentrations (250 and 125 mg/m^3) produced metabolite levels that were nearly identical. The dramatic decrease in metabolites during the first 48 hours post exposure and the similarity of the plots for all three concentrations demonstrate that a very efficient mechanism exists for the metabolism of this material. This conclusion is further supported by the recent isolation purification and characterization of the enzyme pyrethroid carboxyesterase from rat liver microsomes.[4] This enzyme is responsible for in vivo metabolism of esters of chrysanthemic acid such as Permethrin.

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[3]Altman, P. L. and Dittmer, D. S., "Handbook of Respiration and Circulation," p. 95, 1970, FASEB, Bethesda, MD.

[4]Suzuki, T., and J. Miyamoto, "Purification and properties of pyrethroid carboxyesterase in rat liver microsomes," Pesticide Biochemistry and Physiology, 8:186 (1978).

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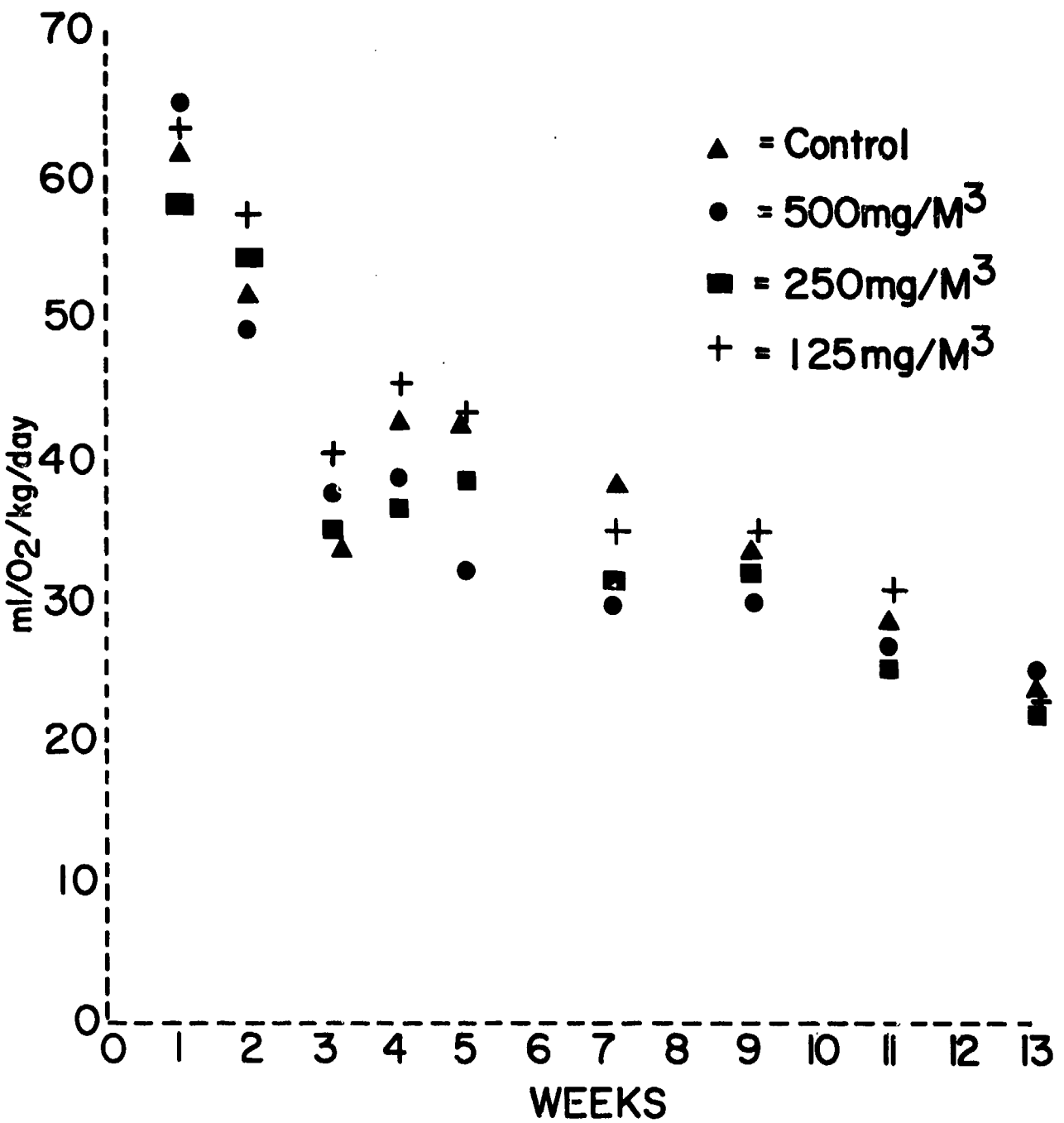
TABLE 15. SUBCHRONIC INHALATION STUDY - SUMMARY OF COMPLIANCE AND RESISTANCE VALUES BEAGLE DOGS

Exposure	Pre-test Compliance ml/cm H_2O/kg Mean ±SD	Post-test Compliance ml/cm H_2O/kg Mean ±SD	Pre-test Resistance cm H_2O/ml/sec/kg Mean & Range ($x10^{-3}$)	Post-test Resistance cm H_2O/ml/sec/kg Mean & Range ($x10^{-3}$)
Control	3.92 ±0.44	4.45 ±2.04	0.90 (0.69-1.2)	1.44 (0.26-2.2)
500 mg/M^3	5.27 ±1.06	3.93 ±2.13	1.29 (0.21-3.12)	2.38 (1.6-3.9)
250 mg/M^3	6.31 ±0.85	4.61 ±2.54	0.33 (0.08-0.56)	1.42 (0.38-4.3)
125 mg/M^3	6.99 2.25	3.95 ±0.04	0.42 (0.13-0.57)	1.63 (1.5-1.9)

FIG. 1 OXYGEN CONSUMPTION-MALE RATS



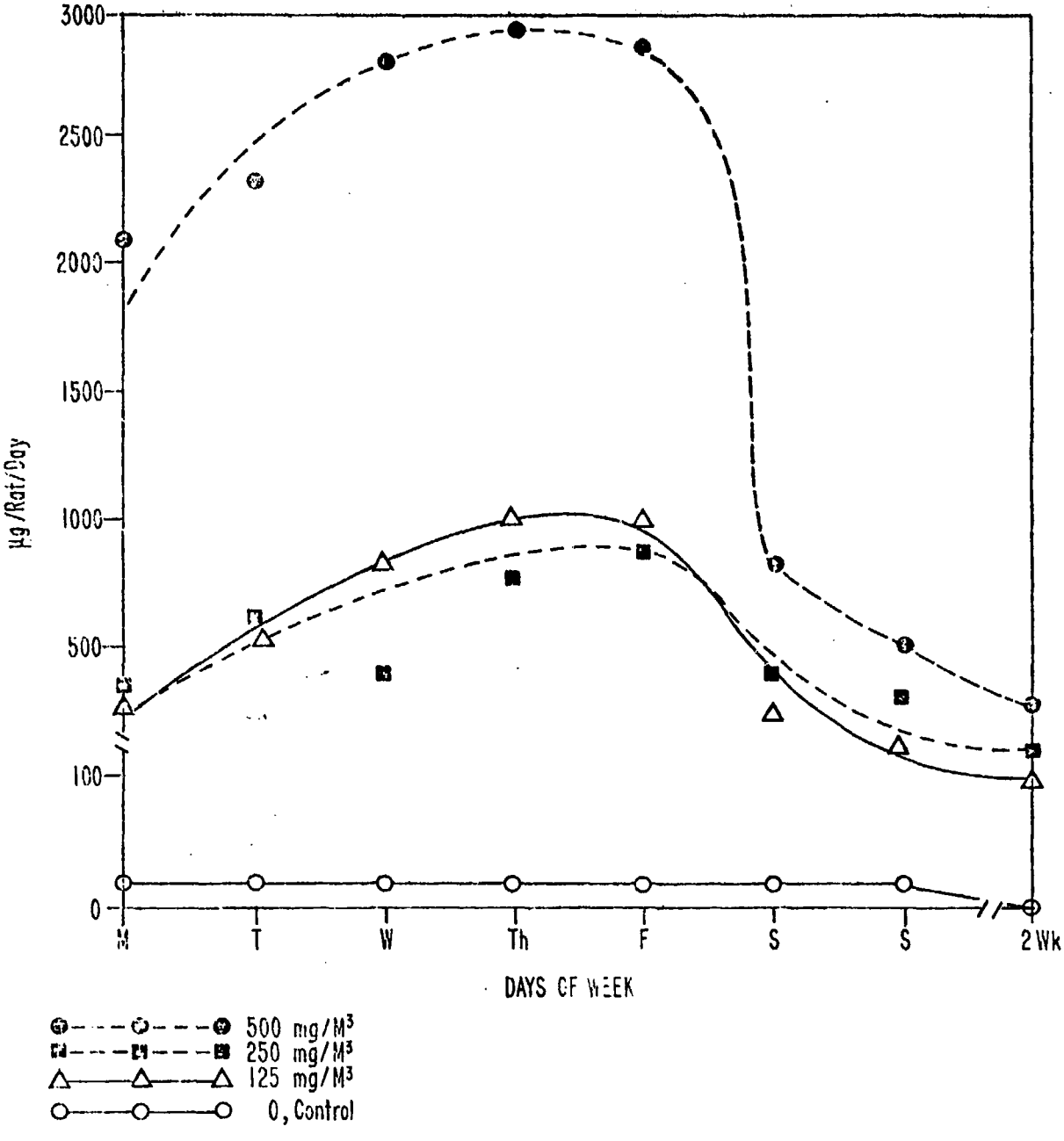


FIGURE 2. PERMETHRIN METABOLITE IN RAT URINE

h. Enzyme Induction Studies. At the conclusion of the 13-week exposure, 10 male rats from each exposure level were tested for enzyme induction. The method employed was a measure of hexobarbital induced sleeping times. All animals were injected intraperitoneally with hexobarbital 220 mg/kg. Sleeping times of the rats were recorded and each exposure group compared to the 10 controls. This study was rerun using the same animals 30 days post exposure. The results are shown in Table 16 and indicate that the group exposed to 500 mg/m^3 of Permethrin had shortened sleeping times, indicating induction of nonspecific liver enzymes, though the effect is not statistically significant at 30 days post exposure or at the lower concentrations.

i. Particle Characterization. A total particle size count was made of the aerosols generated using Teflon® coated slides and a light microscope fitted with a Porton graticule. The slides were affixed to an 18-inch rod and inserted to the center of the exposure chamber for 30 seconds. Slides were withdrawn and particles counted and sized from random sample areas at a magnification of 430 power. A minimum of 200 particles were examined from each slide. Results of these counts indicated that for all three concentrations, 85 percent of the total number of particles had a diameter of 1.0 micron or less. The mass median diameter of the aerosol as determined by a Unico cascade impactor was 5.1 microns. Six-liter air samples were drawn through the five stages of the impactor at a flow rate of 12.0 liters/min. The glass slides from each stage were then analyzed for Permethrin by gas chromatography.

j. Histopathology.

(1) Rats. At the conclusion of the 90-day exposures, half of the rats were submitted for necropsy. Examination of the tissues by light microscopy indicated that no compound related lesions were observed. These data are found in Appendix B. The remaining rats were held for an additional 90 days and then submitted for necropsy. No compound related lesions were observed in this group and these data are found in Appendix C.

(2) Guinea Pigs. All guinea pigs were submitted for necropsy at the conclusion of the 90-day exposure. No exposure related lesions were observed. Results are shown in Appendix D.

(3) Dogs. Exposure related lesions were not observed in male or female beagle dogs necropsied immediately after exposure. Results are shown in Appendix E.

7. DISCUSSION.

a. This 13-week inhalation exposure to Permethrin resulted in only slight toxicity at the highest concentration tested and essentially no toxic

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TABLE 16. ENZYME INDUCTION - HEXOBARBITAL

SLEEPING TIMES - RATS (MALE)

Treatment Group	Sleeping Times (Min) 1-Day Post Exposure	Sleeping Times (Min) 30-Day Post Exposure
500 mg/M^3	44 ± 14*	69 ± 32
250 mg/M^3	65 ± 11	72 ± 10
125 mg/M^3	64 ± 12	74 ± 10
Control	77 ± 19	79 ± 12

* sig at p< .01

reactions were seen at the two lower concentration levels. The rats appeared to be the most susceptible species as they exhibited tremors and convulsions at the 500 mg/m^3 concentration whereas the dogs and guinea pigs showed no toxic signs at any of the concentration levels tested. A marked adaptation to the compound appears to be possible in rats as seen in the rapid disappearance of toxic signs and with no signs being detected after the second week of exposure. Both prior work and this study have shown that this compound is an inducer of hepatic enzymes and as such can probably be handled by the liver with greater efficiency after an initial induction period. Both functional and histological data showed no direct effect on the pulmonary system and oxygen consumption was unaltered. Irritation of the eyes and mucous membranes was not seen in this study and the prolonged exposure to this material did not produce a sensitization reaction. Body weights and organ-to-body weight ratios were unaffected. Clinical chemistries and hematology were all within normal limits.

b. The studies done in this laboratory showed that large doses of the test compound are required to cause toxic responses in animals. Biochemical studies done by this laboratory and others indicated that the material is rapidly metabolized and excreted.

8. CONCLUSION. It is concluded that technical grade SBP 1513 (Permethrin) does not present an acute toxic hazard to man from accidental inhalation or ingestion. Its use as a clothing impregnant should present no toxic hazard to man under normal use conditions.

9. RECOMMENDATIONS. It is recommended that approval be given to the use of the synthetic pyrethroid 3-(Phenoxyphenyl) methyl (±)-cis, trans-3-(2,2-Dichloroethenyl)-2,2-dimethylcyclopropanecarboxylate (SBP 1513, Permethrin) as a clothing impregnant or space repellent.

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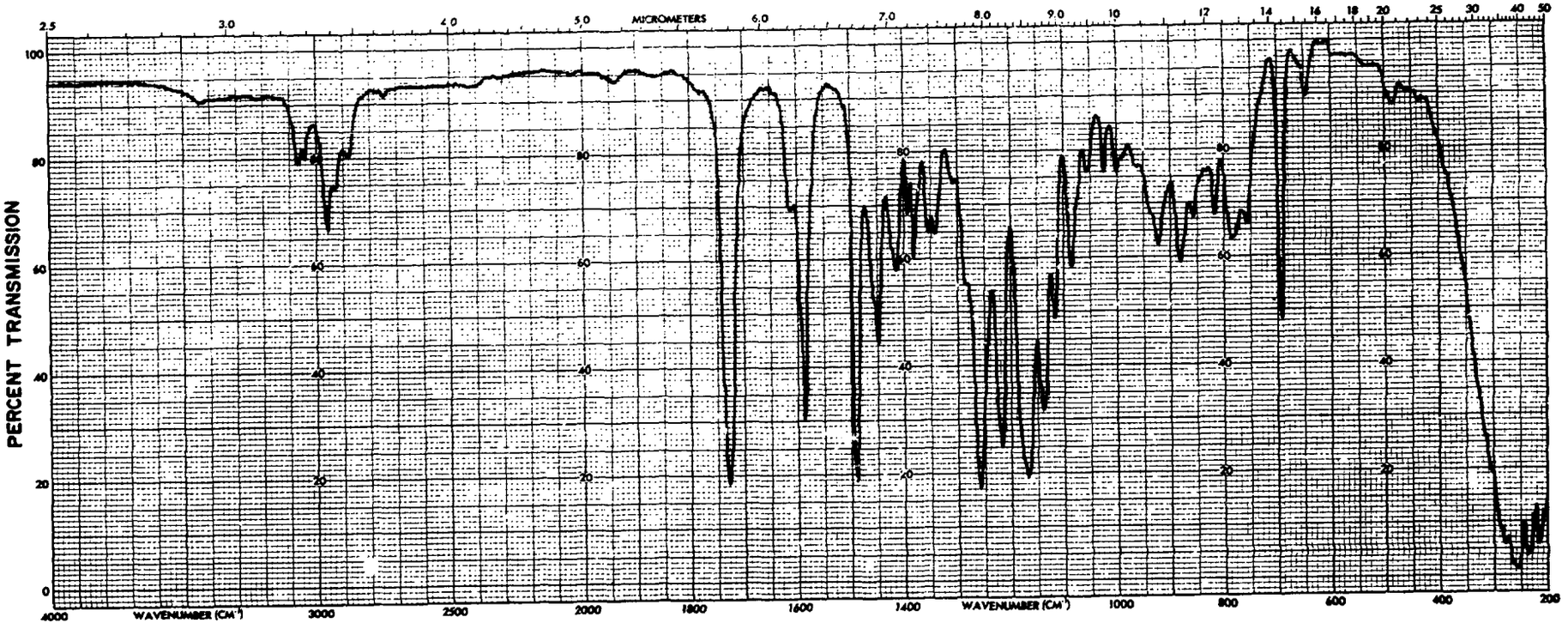
STUDY NO. 75-51-0026-80, MAY-DEC 78

APPENDIX A

INFRARED SPECTRUM



SAMPLE: 3-(PHENOXYPHENYL) METHYL (±)-CIS, TRANS-3-(2,2-DICHLOROETHENYL)-2,2-DIMETHYLCYCLOPROPANECARBOXYLATE (PERMETHRIN) (LOT# RAX-6)

SCAN TIME 24 MIN

SLIT PROGRAM 6

RESPONSE 1

EXPANSION 1

Study No. 75-51-0026-80, May-Dec 78

APPENDIX B

SUMMARY INCIDENCE TABLES

RATS

Necropsy Date: 31 Jul 78 to 1 Aug 78

Compound related lesions were not observed. The lymphoid proliferation and pneumonitis observed in controls and all exposure groups was considered an expression of Chronic Murine Pneumonia that is endemic in most rat colonies. This degree of mycoplasmosis did not compromise the evaluation by light-microscopy of possible exposure related affects.

CONRAD R. POPE, DVM
LTC, VC
Chief, Pathology and Animal Care Branch
Toxicology Division

SUMMARY INCIDENCE TABLE

FEMALES and MALES COMBINED

USAEHA
STUDY NO. 75-51-0026-80
Permethrin

SUBCHRONIC INHALATION Permethrin Rats Necropsy date - 31 July 1978 to 1 August 1978	CONTROLS 0mg/m^3	HIGH 500mg/m^3	MEDIUM 250mg/m^3	LOW 125mg/m^3		
No. of Animals	(20)	(20)	(18)	(20)		
BRAIN (No. Examined)	(18,	(19)	(16)	(19)		
BRAIN STEM (No. Examined)	(19)	(20)	(16)	(19)		
NASAL TURBINATES (No. Examined)	(20)	(19)	(16)	(18)		
TRACHEA (No. Examined)	(9)	(15)	(10)	(10)		
Lymphoid proliferation	8	13	9	7		
LUNG (No. Examined)	(19)	(20)	(17)	(20)		
Lymphoid proliferation	19	20	17	20		
Pneumonitis, diffuse	3	4		2		
Pneumonitis, focal	2	1	1			
Chronic Murine Pneumonia		1	1	1		
Macrophages, focal						
Macrophages, multi-focal		1	1			
EYES (No. Examined)	(20)	(20)	(17)	(20)		
LIVER (No. Examined)	(20	(20)	(17)	(20)		
KIDNEY (No. Examined)	(20)	(20)	(17)	(19)		
SCIATIC NERVE (No. Examined)	(18)	(17)	(17)	(20)		

SUMMARY INCIDENCE TABLE

MALES

USAEHA
STUDY NO. 75-51-0026-80
Permethrin

SUBCHRONIC AEROSOL INHALATION Permethrin Rats Necropsy date - 1 Aug 78	CONTROL 0 mg/m^3	HIGH 500mg/m^3	MEDIUM 250mg/m^3	LOW 125mg/m^3		
No. of Animals	(10)	(10)	(10)	(10)		
BRAIN (No. Examined)	(8)	(9)	(8)	(10)		
BRAIN STEM (No. Examined)	(9)	(10)	(8)	(9)		
NASAL TURBINATES (No. Examined)	(10)	(10)	(8)	(9)		
TRACHEA (No. Examined)	(6)	(7)	(3)	(5)		
Lymphoid proliferation	5	6	3	5		
LUNG (No. Examined)	(10)	(10)	(9)	(10)		
Lymphoid proliferation	10	10	9	10		
Pneumonitis, diffuse	3	4		2		
Pneumonitis, focal			1			
Chronic Murine Pneumonia			1			
Macrophages, focal						
Macrophages, multi-focal			1			
EYES (No. Examined)	(10)	(10)	(9)	(10)		
LIVER (No. Examined)	(10)	(10)	(9)	(10)		
KIDNEY (No. Examined)	(10)	(10)	(9)	(9)		
SCIATIC NERVE (No. Examined)	(8)	(8)	(9)	(10)		

SUMMARY INCIDENCE TABLE

FEMALES

USAEHA
STUDY NO. 75-51-0026-80
Permethrin

SUBCHRONIC AEROSOL INHALATION Permethrin Rats Necropsy date - 31 July 1978	CONTROLS 0mg/m^3	HIGH 500mg/m^3	MEDIUM 250mg/m^3	LOW 125mg/m^3		
No. of Animals	(10)	(10)	(8)	(10)		
BRAIN (No. Examined)	(10)	(10)	(8)	(9)		
BRAIN STEM (No. Examined)	(10)	(10)	(8)	(10)		
NASAL TURBINATES (No. Examined)	(10)	(9)	(8)	(9)		
TRACHEA (No. Examined)	(3)	(8)	(7)	(5)		
Lymphoid proliferation	3	7	6	2		
LUNG (No. Examined)	(9)	(10)	(8)	(10)		
Lymphoid proliferation	9	10	8	10		
Pneumonitis, diffuse						
Pneumonitis, focal	2	1				
Chronic Murine Pneumonia	1	1		1		
Macrophages, focal						
Macrophages, multi-focal		1				
EYES (No. Examined)	(10)	(10)	(8)	(10)		
LIVER (No. Examined)	(10)	(10)	(8)	(10)		
KIDNEY (No. Examined)	(10)	(10)	(8)	(10)		
SCIATIC NERVE (No. Examined)	(10)	(9)	(8)	(10)		
		B-5				

HISTOPATHOLOGY INCIDENCE TABLE

Controls 0 mg/m^3

USAEHA
STUDY NO. 75-51-0026-80
SUBCHRONIC INHALATION TOXICITY
Permethrin
Rats

PB NO	Females (necropsy date 31 Jul 78)										Males (necropsy date 1 Aug 78)									
	545	546	547	548	549	550	551	552	553	554	585	586	587	588	589	590	591	592	593	594
BRAIN	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	N	X	X	X	N
BRAIN STEM	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	N
NASAL TURBINATES	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
TRACHEA		N	N		N	N	N	N	N					N	N		N	N		X
Lymphoid proliferation	2			3						3	3	2	3			3			3	
LUNG	N																			
Lymphoid proliferation		2	2	2	2	3	2	3	2	2	2	4	2	4	2	3	3	3-4	3-4	2
Pneumonitis, diffuse														2		2			2	
Pneumonitis, focal						2		2												
Chronic Murine Pneumonia					3															
Macrophages, focal																				
Macrophages, multi-focal																				
EYES	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
LIVER	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
KIDNEY	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
SCIATIC NERVE	X	X	X	X	X	X	X	X	X	X	X	X	X	N	X	X	X	N	X	X

KEY

X = not remarkable
N = no section
1 = rare
2 = minimal
3 = moderate
4 = severe
3-4 = moderate to severe

HISTOPATHOLOGY INCIDENCE TABLE

500 mg/m^3

USAEHA
STUDY NO. 75-51-0026-80
SUBCHRONIC INHALATION TOXICITY
Permethrin
Rats

	Females (necropsy date 31 Jul 78)															Males (necropsy date 1 Aug 78)														
PB NO	555	556	557	558	559	560	561	562	563	564						595	596	597	598	599	600	601	602	603	604						
BRAIN	X	X	X	X	X	X	X	X	X	X						X	N	X	X	X	X	X	X	X	X						
BRAIN STEM	X	X	X	X	X	X	X	X	X	X						X	X	X	X	X	X	X	X	X	X						
NASAL TURBINATES	X	X	X	N	X	X	X	X	X	X						X	X	X	X	X	X	X	X	X	X						
TRACHEA		N				N				N									X	N		N			N						
Lymphoid proliferation	2		2	3	2		1	3	2							2	2	2			1		1	2							
LUNG																														
Lymphoid proliferation	2	1	2	2	2	1	1	3	3	3						3	2	2	2	2	3	3	3	2	2						
Pneumonitis, diffuse						2		3												2	1		1		2						
Pneumonitis, focal																														
Chronic Murine Pneumonia																														
Macrophages, multi-focal										2																				
EYES	X	X	X	X	X	X	X	X	X	X						X	X	X	X	X	X	X	X	X	X						
LIVER	X	X	X	X	X	X	X	X	X	X						X	X	X	X	X	X	X	X	X	X						
KIDNEY	X	X	X	X	X	X	X	X	X	X						X	X	X	X	X	X	X	X	X	X						
SCIATIC NERVE	X	X	X	X	X	X	X	X	X	N						X	X	X	X	N	X	X	X	N	X						

KEY

X = not remarkable
N = no section
1 = rare
2 = minimal
3 = moderate
4 = severe

HISTOPATHOLOGY INCIDENCE TABLE
250 mg/m³

USAEHA
STUDY NO. 75-51-0026-80
SUBCHRONIC INHALATION TOXICITY
Permethrin
Rats

PB NO	Female (necropsy date 31 Jul 78)											Males (necropsy date 1 Aug 78)									
	565	566	567	568	569	570	571	572	573	574		605	606	607	608	609	610	611	612	613	614
BRAIN	X	X	X	X	X	X	N	X	N	X		X	X	X	X	N	X	X	N	N	X
BRAIN STEM	X	X	X	X	X	X	N	X	N	X		X	X	X	X	N	X	X	N	N	X
NASAL TURBINATES	X	X	X	X	X	X	N	X	N	X		X	X	X	X	N	X	X	X	N	X
TRACHEA				N		X	N		N				N		N	N	N	N		N	N
Lymphoid proliferation	1	2	1		1			3		1		2		2					1		
LUNG							N		N											N	
Lymphoid proliferation	2	3	2	3	2	2		4		2		2	2	2	2	2	1	2	2		3
Pneumonitis, diffuse																					
Pneumonitis, focal																		2			
Chronic Murine Pneumonia																					3
Macrophages, multi-focal																	2				
EYES	X	X	X	X	X	X	N	X	N	X		X	X	X	X	X	X	X	X	N	X
LIVER	X	X	X	X	X	X	N	X	N	X		X	X	X	X	X	X	X	X	N	X
KIDNEY	X	X	X	X	X	X	N	X	N	X		X	X	X	X	X	X	X	X	N	X
SCIATIC NERVE	X	X	X	X	X	X	N	X	N	X		X	X	X	X	X	X	X	X	N	X

KEY

X = not remarkable
N = no section
1 = rare
2 = minimal
3 = moderate
4 = severe

HISTOPATHOLOGY INCIDENCE TABLE

125 mg/m^3

USAEHA
STUDY NO. 75-51-0025-80
SUBCHRONIC INHALATION TOXICITY
Permethrin
Rats

PB NO	Females (necropsy date 31 Jul 78)										Males (necropsy date 1 Aug 78)									
	575	576	577	578	579	580	581	582	583	584	615	616	617	618	619	620	621	622	623	624
BRAIN	X	X	X	X	N	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
BRAIN STEM	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	N
NASAL TURBINATES	N	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	N	X
TRACHEA	N	N	N	N	N			X	X	X						N	N	N	N	N
Lymphoid proliferation						2	1				2	3	3	3	1					
LUNG																				
Lymphoid proliferation	4	2	2	2	4	4	3	2	2	2	2	2	2	3	4	3	2	2	2	2
Pneumonitis, diffuse															1	2				
Pneumonitis, focal																				
Chronic Murine Pneumonia		3																		
Macrophages, multi-focal																				
EYES	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
LIVER	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
KIDNEY	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	N	X	X
SCIATIC NERVE	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X

KEY

X = not remarkable
N = no section
1 = rare
2 = minimal
3 = moderate
4 = severe

Study No. 75-51-0026-80, May-Dec 78

APPENDIX C

SUMMARY INCIDENCE TABLES

RATS

90 DAY POST EXPOSURE

Necropsy Date: 2 Nov 78

COMMENTS:

Exposure related lesions were not recognized.

The respiratory lesions were an expression of endemic respiratory tract mycoplasma infection. The lesions were not of sufficient severity to compromise light-microscopic evaluation.

The kidney lesions were not considered compound related but an expression of early spontaneous kidney disease common to the rat.

CONRAD R. POPE, DVM
LTC, VC
Chief, Pathology and Animal Care Branch
Toxicology Division

SUMMARY INCIDENCE TABLE

FEMALE

USAEHA
STUDY NO. 75-51-0026-80
Permethrin

SUBCHRONIC INHALATION Permethrin Rats Necropsy date - 2 Nov 78	CONTROLS 0mg/m^3	HIGH 500mg/m^3	MEDIUM 250mg/m^3	LOW 125mg/m^3		
No. of Animals	(10)	(9)	(10)	(10)		
BRAIN (No. Examined)	(8)	(9)	(10)	(10)		
BRAIN STEM (No. Examined)	(8)	(9)	(10)	(10)		
NASAL TURBINATES (No. Examined)	(10)	(9)	(10)	(10)		
TRACHEA (No. Examined)	(10)	(9)	(10)	(10)		
Lymphoid proliferation	10	8	8	10		
Micro-abscess			1			
LUNG (No. Examined)	(10)	(8)	(10)	(10)		
Lymphoid proliferation	10	8	10	10		
Pneumonitis, diffuse	2	2	2			
Pneumonitis, focal	1		1			
Chronic Murine Pneumonia		1				
Macrophages, focal						
Macrophages, multi-focal						
EYES (No. Examined)	(10)	(8)	(10)	(10)		
LIVER (No. Examined)	(10)	(9)	(10)	(10)		
KIDNEY (No. Examined)	(10)	(10)	(10)	(10)		
Nephrocalcinosis		1				
SCIATIC NERVE (No. Examined)	(10)	(9)	(0)	(0)		

SUMMARY INCIDENCE TABLE

MALES

USAEPA
STUDY NO. 75-51-0026-80
Permethrin

SUBCHRONIC INHALATION Permethrin Rats Necropsy date - 1 Nov 78	CONTROLS 0mg/m^3	HIGH 500mg/m^3	MEDIUM 250mg/m^3	LOW 125mg/m^3		
No. of Animals	(9)	(8)	(10)	(10)		
BRAIN (No. Examined)	(9)	(6)	(7)	(6)		
BRAIN STEM (No. Examined)	(9)	(5)	(5)	(7)		
NASAL TURBINATES (No. Examined)	(8)	(6)	(8)	(8)		
TRACHEA (No. Examined)	(2)	(4)	(5)	(5)		
Lymphoid proliferation	2	3	5	4		
LUNG (No. Examined)	(9)	(8)	(10)	(10)		
Lymphoid proliferation	9	8	9	8		
Pneumonitis, diffuse	1		1	2		
Pneumonitis, focal						
Chronic Murine Pneumonia						
Macrophages, focal	1	1				
Macrophages, multi-focal						
EYES (No. Examined)	(6)	(8)	(9)	(8)		
LIVER (No. Examined)	(8)	(9)	(10)	(9)		
KIDNEY (No. Examined)	(9)	(8)	(10)	(9)		
Interstitial nephritis		2	1	1		
SCIATIC NERVE (No. Examined)	(0)	(0)	(0)	(0)		

SUMMARY INCIDENCE TABLE

FEMALES and MALES COMBINED

USAMRIID
STUDY NO. 75-51-0026-80
Permethrin

SUBCHRONIC INHALATION Permethrin Rats Necropsy date 1-2 Nov 78	CONTROLS 0mg/m^3	HIGH 500mg/m^3	MEDIUM 250mg/m^3	LOW 125mg/m^3		
No. of Animals	(19)	(17)	(20)	(20)		
BRAIN (No. Examined)	(17)	(15)	(17)	(16)		
BRAIN STEM (No. Examined)	(17)	(14)	(15)	(17)		
NASAL TURBINATES (No. Examined)	(18)	(15)	(18)	(18)		
TRACHEA (No. Examined)	(12)	(13)	(15)	(15)		
Lymphoid proliferation	12	11	13	14		
Micro-abscess			1			
LUNG (No. Examined)	(19)	(16)	(20)	(20)		
Lymphoid proliferation	19	16	19	18		
Pneumonitis, diffuse	3	2	3	2		
Pneumonitis, focal	1		1			
Chronic Murine Pneumonia		1				
Macrophages, focal	1	1				
Macrophages, multi-focal						
EYES (No. Examined)	(16)	(16)	(19)	(18)		
LIVER (No. Examined)	(18)	(18)	(20)	(19)		
KIDNEY (No. Examined)	(19)	(18)	(20)	(19)		
Nephrocalcinosis		1				
Interstitial nephritis		2	1	1		
SCIATIC NERVE (No. Examined)	(10)	(9)	(0)	(0)		
			C-5			

HISTOPATHOLOGY INCIDENCE TABLE

Controls 0 mg/m^3

USAEHA
STUDY NO. 75-51-0026-80
SUBCHRONIC INHALATION TOXICITY
Permethrin
Rats

	Females (necropsy date 2 Nov 78)										Males (necropsy date 1 Nov 78)								
PB NO	982	983	984	985	986	987	988	989	900	901	944	945	946	947	948	949	950	951	952
BRAIN	X	X	N	X	X	X	X	N	X	X	X	X	X	X	X	X	X	X	X
BRAIN STEM	X	X	N	X	X	X	X	N	X	X	X	X	X	X	X	X	X	X	X
NASAL TURBINATES	X	X	X	X	X	X	X	X	X	X	X	X	X	X	N	X	X	X	X
TRACHEA		N			N			X	N		N	N	N	N	N	N	N		
Lymphoid proliferation	2		2	2		2	1			1								1	3
LUNG																			
Lymphoid proliferation	1	3	2	2	1	3	2	3	4	3	2	2	2	2	2	2	1	2	2
Pneumonitis, diffuse						2		4							2				
Pneumonitis, focal																			
Chronic Murine Pneumonia																		1	
Macrophages, focal																			
Macrophages, multi-focal			1																
EYES	X	X	X	X	X	X	X	X	X	X	N	N	X	X	X	X	X	X	N
LIVER	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	N	X	X	X
KIDNEY	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	N	X	X	X
Nephrocalcinosis																			
Interstitial nephritis																			
SCIATIC NERVE	X	X	X	X	X	X	X	X	X	X	N	N	N	N	N	N	N	N	N	N

KEY

X = not remarkable
N = no section
1 = rare
2 = minimal
3 = moderate
4 = severe

HISTOPATHOLOGY INCIDENCE TABLE

125 mg/m^3

USAEHA
STUDY NO. 75-51-0026-80
SUBCHRONIC INHALATION TOXICITY
Permethrin
Rats

PB NO	Females (necropsy date 2 Nov 78)										Males (necropsy date 1 Nov 78)									
	972	973	974	975	976	977	978	979	980	981	934	935	936	937	938	939	940	941	942	943
BRAIN	X	X	X	X	X	X	X	X	X	X	X	N	N	X	X	N	X	X	X	N
BRAIN STEM	X	X	X	X	X	X	X	X	X	X	X	N	N	X	X	X	X	X	X	N
NASAL TURBINATES	X	X	X	X	X	X	X	X	X	X	X	X	X	N	X	X	X	X	X	N
TRACHEA											X		N	N	N	N	N			
Lymphoid proliferation	3-4	4	2	2	2	2	2	3	3	1		4						2	3	3
LUNG											X		X							
Lymphoid proliferation	2	2	2	3	2	2	2	1	2	2		1		2	2	2	2	2	2	2
Pneumonitis, diffuse																2	2			
Pneumonitis, focal																				
Chronic Murine Pneumonia																				
Macrophages, multi-focal																				
EYES	X	X	X	X	X	X	X	X	X	X	X	X	X	N	X	X	X	N	X	X
LIVER	X	X	X	X	X	X	X	X	X	X	N	X	X	X	X	X	X	X	X	X
KIDNEY	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X		X	X	X
Nephrocalcinosis																				
Interstitial nephritis																	3			
SCIATIC NEPVE	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N

KEY

X = not remarkable
N = no section
1 = rare
2 = minimal
3 = moderate
4 = severe
3-4 = moderate to severe

HISTOPATHOLOGY INCIDENCE TABLE

250 mg/m^3

USAEHA
STUDY NO. 75-51-0026-80
SUBCHRONIC INHALATION TOXICITY
Permethrin
Rats

PR NO	Females (necropsy date 2 Nov 78)										Males (necropsy date 1 Nov 78)									
	962	963	964	965	966	967	968	969	970	971	924	925	926	927	928	929	930	931	932	933
BRAIN	X	X	X	X	X	X	X	X	X	X	N	X	X	X	N	X	X	X	X	N
BRAIN STEM	X	X	X	X	X	X	X	X	X	X	N	X	N	X	N	X	X	X	N	N
NASAL TURBINATES	X	X	X	X	X	X	X	X	X	X	N	X	X	X	X	X	X	X	X	N
TRACHEA		X				N					N	N	N						N	N
Lymphoid proliferation	1		2	3	2		2	2	3	1				3	3	3	3	3		
Micro-abscess			2																	
LUNG												X								
Lymphoid proliferation	2	2	3	2	3	3	2	3	2	3	2		3	3	3	2	3	3	2	2
Pneumonitis, diffuse	2					1								2-3						
Pneumonitis, focal						4														
Chronic Murine Pneumonia																				
Macrophages, focal																				
Macrophages, multi-focal																				
EYES	X	X	X	X	X	X	X	X	X	X	N	X	X	X	X	X	X	X	X	X
LIVER	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
KIDNEY	X	X	X	X	X	X	X	X	X	X	X	X	X		X	X	X	X	X	X
Nephrocalcinosis																				
Interstitial nephritis														2						
SCIATIC NERVE	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N

KEY

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N = no section
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4 = severe
2-3 = minimal to moderate

HISTOPATHOLOGY INCIDENCE TABLE

500 mg/m^3

USAEHA
STUDY NO. 75-51-0026-80
SUBCHRONIC INHALATION TOXICITY
Permethrin
Rats

PB NO	Females (necropsy date 2 Nov 78)									Males (necropsy date 1 Nov 78)							
	953	954	955	956	957	958	959	960	961	916	917	918	919	920	921	922	923
BRAIN	X	X	X	X	X	X	X	X	X	X	N	X	X	N	X	X	X
BRAIN STEM	X	X	X	X	X	X	X	X	X	X	N	X	X	N	X	X	N
NASAL TURBINATES	X	X	X	X	X	X	X	X	X	X	X	X	X	X	N	X	N
TRACHEA	X	X	N	X	X				N	X			N	N	N	N	
Lymphoid proliferation						3	3	3			4	3					3
LUNG			N														
Lymphoid proliferation	2	2		2	1	3	2	1	1	2	2	2	2	3	2	1	2
Pneumonitis, diffuse																	
Pneumonitis, focal																	
Chronic Murine Pneumonia							3										
Macrophages, focal																	2
Macrophages, multi-focal																	
EYES	X	X	N	X	X	X	X	X	X	X	X	X	X	X	X	X	X
LIVER	X	X	X	X	X	X	X	X	X	X	X	X	X	N	X	X	X
KIDNEY		X	X	X	X	X	X	X	X	X		X	X	X	X	X	
Nephrocalcinosis	1																
Interstitial nephritis											2						2
Sciatic nerve	X	X	X	X	X	X	X	X	X	X	N	N	N	N	N	N	N

KEY

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4 = severe

Study No. 75-51-0026-80, May-Dec 78

APPENDIX D

SUBCHRONIC INHALATION

GUINEA PIGS

SUBCHRONIC INHALATION

GUINEA PIGS - Males

USAEHA
Study No. 75-51-0026-80
Permethrin

COMMENTS:

Exposure related lesions were not observed.

Low grade respiratory disease was present in both exposed and control animals. The resultant lesions were not extensive or severe enough to compromise light-microscopic evaluation of possible compound related respiratory affects.

The interstitial nephritis was not considered to be compound related. This lesion was not seen in control animals. The reasons that this pathologist did not view this lesion as compound related were (1) there was no dose response relationship among the three exposure groups (2) there was no evidence of a toxic tubular nephrosis (3) interstitial nephritis of this type and degree are not infrequently seen spontaneously in guinea pigs.

CONRAD R. POPE, DVM
LTC, VC
Chief, Pathology and Animal Care Branch
Toxicology Division

SUMMARY INCIDENCE TABLE - Guinea Pig-Males

SUBCHRONIC INHALATION TOXICITY

USAEHA
STUDY NO. 75-51-0026-80
Permethrin

	CONTROL	500 mg/m^3	250 mg/m^3	125 mg/m^3		
Brain (No. Examined)	(8)	(9)	(10)	(8)		
Eye (No. Examined)	(7)	(9)	(10)	(8)		
Nasal Turbinates (No. Examined)	(2)	(9)	(9)	(8)		
Purulent rhinitis			1			
Trachea	(8)	(9)	(10)	(8)		
Lymphoid proliferation	2					
Lung (No. Examined)	(8)	(9)	(10)	(8)		
Lymphoid proliferation	8	9	10	8		
Interstitial pneumonia	6	9	10	8		
Mucopurulent bronchiolar plug			1			
Liver (No. Examined)	(8)	(9)	(10)	(8)		
Kidney (No. Examined)	(8)	(9)	(9)	(8)		
Nephrocalcinosis	2	6	2			
Interstitial nephritis		2	4	6		

HISTOPATHOLOGY INCIDENCE TABLE

USAEHA
STUDY NO. 75-51-0026-80
SUBCHRONIC INHALATION TOXICITY
Permethrin
Guinea Pigs - Male

PB NO.	250 mg/m³															125 mg/m³																	
	661	662	663	664	665	666	667	668	669	670						671	672	673	674	675	676	677	678	679	680								
BRAIN	X	X	X	X	X	X	X	X	X	X						X	X	X	X	N	N	X	X	X	X								
EYE	X	X	X	X	X	X	X	X	X	X						X	X	X	X	N	N	X	X	X	X								
NASAL TURBINATES	X	X	X	X	X	N	X	X		X						X	X	X	X	N	N	X	X	X	X								
Purulent rhinitis									2																								
TRACHEA	X	X	X	X	X	X	X	X	X	X						X	X	X	X	N	N	X	X	X	X								
Lymphoid proliferation																				N	N												
LUNG																																	
Lymphoid proliferation	2	2	2	2	3	3	2	2	2	2						3	2	2	2			1	3	2	2								
Interstitial pneumonia	1	1	3	2	3	3	3	2	3	1						2	2	2-3	3			2	3	2	3								
Mucopurulent bronchiolar plug								2																									
LIVER	X	X	X	X	X	X	X	X	X	X						X	X	X	X	N	N	X	X	X	X								
KIDNEY	X					X		X		N										N	N		X										
Nephrocaleinosis		1		1												1		1	1			1											
Interstitial nephritis			1		1		1		1								2	1	1			1		1	1								

KEY

X = not remarkable
N = no section
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3 = moderate
2-3 = minimal to moderate

HISTOPATHOLOGY INCIDENCE TABLE

USAEHA
STUDY NO. 75-51-0026-80
SUBCHRONIC INHALATION TOXICITY
Permethrin
Guinea Pigs - Male

PD NO.	CONTROLS 0mg/m³										500 mg/m³									
	641	642	643	644	645	646	647	648	649	650	651	652	653	654	655	656	657	658	659	660
BRAIN	X	X	X	X	X	X	N	X	N	X	X	X	X	X	X	X	X	X	N	X
EYE	N	X	X	X	X	X	N	X	N	X	X	X	X	X	X	X	X	X	N	X
NASAL TURBINATES	N	N	X	N	N	X	N	N	N	N	X	X	X	X	X	X	X	X	N	X
TRACHEA	X	X	X		X	X	N	X	N		X	X	X	X	X	X	X	X	N	X
Lymphoid proliferation				1						2										
LUNG							N		N										N	
Lymphoid proliferation	1	2	2	2	2	3		2		1	2	3	2	2	1	2	2	2		2
Interstitial pneumonia		3	1		1	2		2		1	2	1	1	1	1	1	1	1		1
Mucopurulent bronchiolar plug																				
LIVER	X	X	X	X	X	X	N	X	N	X	X	X	X	X	X	X	X	X	N	X
KIDNEY	X	X			X	X	N	X	N	X	X	X	X	X	X	X	X	X	N	X
Nephrocalcinosis			1	1							1	1			1		1	1		1
Interstitial nephritis												1								1

KEY

X = not remarkable
N = no section
1 = rare
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3 = moderate

Study No. 75-51-0026-80, May-Dec 78

APPENDIX E

SUBCHRONIC INHALATION

DOGS

SUBCHRONIC INHALATION

DOGS

USAEHA
Study No. 75-51-0026-80
Permethrin

COMMENTS:

Exposure related lesions were not observed in female or male Beagle dogs.

The pneumonitis and pneumonia that were observed microscopically in both control and exposed animals was subclinical. The microscopic findings gave evidence that both male and female dogs had chronic subclinical respiratory disease.

It is this pathogist's opinion that the respiratory disease that was present did not prevent meaningful light-microscopic evaluation of possible compound related respiratory affects.

CONRAD R. POPE, DVM
LTC, VC
Chief, Pathology and Animal Care Branch
Toxicology Division

SUMMARY INCIDENCE TABLE - Dogs-Male

SUBCHRONIC INHALATION

USAEHA
STUDY NO. 75-51-0026-80
Permethrin

	CONTROL	500 mg/m^3	250 mg/m^3	125 mg/m^3		
Brain (No. Examined)	(2)	(2)	(2)	(2)		
Eye (No. Examined)	(2)	(2)	(2)	(2)		
Nasal Turbinates (No. Examined)	(2)	(2)	(2)	(2)		
Trachea (No. Examined)	(2)	(2)	(2)	(2)		
Lung (No. Examined)	(2)	(2)	(2)	(2)		
Pneumonitis	2	2	2	2		
Pneumonitis with						
epithelialization	1					
Purogranulomatous						
pneumonia		1				
Granulomatous pneumonia			1			
Bronhopneumonia				1		
Liver (No. Examined)	(2)	(2)	(2)	(2)		
Kidney (No. Examined)	(2)	(2)	(2)	(2)		

SUMMARY INCIDENCE TABLE - Dogs-Female

SUBCHRONIC INHALATION

USAEHA
STUDY NO. 75-51-0026-80
Permethrin

	CONTROL	500 mg/m^3	250 mg/m^3	125 mg/m^3		
Brain (No. Examined)	(2)	(2)	(2)	(2)		
Eye (No. Examined)	(2)	(2)	(2)	(2)		
Nasal Turbinates (No. Examined)	(1)	(2)	(2)	(1)		
Trachea (No. Examined)	(2)	(2)	(2)	(2)		
Lung (No. Examined)	(2)	(2)	(2)	(2)		
Pneumonitis	1	1	1	1		
Pneumonitis with						
epithelialization	1					
Purogranulomatous pneumonia	1					
Granulomatous pneumonia		1	2	1		
Liver (No. Examined)	(2)	(2)	(2)	(2)		
Kidney (No. Examined)	(2)	(2)	(2)	(2)		
Interstitial nephritis			1			

HISTOPATHOLOGY INCIDENCE TABLE

(Exposure Level)

USAEHA
STUDY NO. 75-51-0026-80
SUBCHRONIC INHALATION TOXICITY
Permethrin
Beagle Dogs

PB NO.	CONTROLS				500 mg/m^3				250 mg/m^3				125 mg/m^3			
	625F	626F	633M	634M	627F	628F	635M	636M	629F	630F	637M	638M	631F	632F	639M	640M
BRAIN	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
EYE	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
NASAL TURBINATES	X	N	X	X	X	X	X	X	X	X	X	X	N	X	X	X
TRACHEA	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
LUNG													X			
Pneumonitis	1		1	2-3		2	2	2	2		2	2		2	4	2
Pneumonitis with epithelialization		2		2												
Purogranulomatous pneumonia		2						2						2		1
Granulomatous pneumonia					1				1	1	1					
LIVER	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
KIDNEY	X	X	X	X	X	X	X	X	X	X	X	X	X		X	X
Interstitial nephritis														1		

KEY

X = not remarkable
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1 = rare
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2-3 = minimal to moderate